IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Richard W. Armentrout
Application No.	:	10/718,488
Filed	:	November 20, 2003
For	:	DNA IN THE PRESENCE OF GELLAN

Examiner	:	Susan Emily Fernandez
Art Unit	:	1651
Docket No.	:	850136.422
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PRE-APPEAL BRIEF REQUEST FOR REVIEW - REMARKS

This request for pre-appeal review is in response to the Final Office Action mailed by the United States Patent and Trademark Office (hereinafter "PTO") on October 7, 2008. A Response after Final was submitted on February 9, 2009, including applicant's request for entry of an amendment to place the application in condition for allowance, but no Action has since issued from the PTO. In the absence of any Advisory Action from the PTO, consideration of applicant's submission of February 9, 2009, is respectfully requested.

Claims 16 and 17 stand finally rejected under 35 U.S.C. § 103(a) for alleged obviousness over Mitra et al. (*Nucleic Acids Research* 27(24)e34: i-iv, 1999) in view of Cole et al. (*BioTechniques* 26:748-756, 1999). The PTO asserts that Mitra et al. teach an amplification reaction in polymerized acrylamide, and that Cole et al. teach the use of gellan as a separation medium for electrophoresis. The PTO then asserts (Action at page 3, third paragraph) that it would have been obvious to substitute the gellan of Cole et al. for the acrylamide of Mitra et al. to arrive at the presently claimed subject matter, and alleges that a person skilled in the art at the time of invention would have been motivated to make such a substitution, since gellan (i) is an alternative gel material that allows easy DNA recovery, (ii) requires low concentrations for gel formation, and (iii) reversibly forms gels.

The PTO clearly errs where the Office Action is silent with respect to the question of what knowledge in the prior art would have led the ordinarily skilled artisan to expect *any* nucleic acid amplification reaction, much less a nucleic acid amplification reaction of enhanced sensitivity, to proceed in the presence of gellan at a concentration above 0.005% wt%. None of the alleged "reasons" (items (i)-(iii) above) to substitute gellan for acrylamide have anything to do with a nucleic acid amplification *reaction*, and certainly are not in any way predictive of such a reaction of *enhanced sensitivity*. Clear teachings of the unexpected ability of gellan to enhance the sensitivity of a nucleic acid amplification reaction appear for the first time in the present application as originally filed, for example, in the specification at page 7, lines 2-4; at page 5, lines 7-10; at page 2, lines 1-18; at page 5, line 25 through page 6, line 6; and elsewhere.

The PTO fails to set forth any evidence that the prior art in any way teaches or suggests the use of gellan to enhance the sensitivity of a nucleic acid amplification reaction, and if anything the prior art teaches away from inclusion of gellan in any nucleic acid amplification reaction mixture. The Examiner's allegations (items (i)-(iii) above) are beside the point, because none of these properties would have provided the ordinarily skilled person with a reasonable expectation of successfully predicting that inclusion of gellan in a nucleic acid amplification reaction would result in a reaction mixture that is capable of amplifying a lower level of target nucleic acid than would be the case if gellan were not present.

The PTO therefore impermissibly employs hindsight in its assertion of the obviousness rejection. In this regard, based on the prior art teachings, which are limited to descriptions of gellan merely as an electrophoresis medium suitable for separation of nucleic acids, gellan would be no more expected to substitute for acrylamide in the reaction of Mitra et al. than would any other known media for nucleic acid electrophoresis, such as agar, agarose, starch, polydextran, or other media. The PTO fails to provide evidence or reasoning as to why the skilled person would have expected predictably and successfully to arrive at a nucleic acid amplification of enhanced sensitivity by including gellan, absent the disclosure of the present application.

The PTO also errs in its assertion (Action, page 3, fourth paragraph) that a claimed property is inherently present in the prior art. Mere use of gellan as an electrophoretic

separation medium in the prior art does not establish the obviousness of its use in nucleic acid amplification reactions to enhance sensitivity. The PTO fails to satisfy the burden that it is *required* to meet, of showing why an allegedly inherent characteristic of the claimed subject matter *necessarily* flows from the prior art *and would have been recognized* by persons having ordinary skill in the art. On this point it is noted that the outstanding rejection is for obviousness, not novelty, such that when the subject matter of the claim is considered *as a whole*, as is properly required, the presently claimed composition did not exist in the prior art and thus the allegedly inherent property cannot have been recognized in a prior art composition. The PTO is referred to Applicant's submission of February 9, 2009, at the last paragraph on page 8 through page 10, for a discussion of why the Examiner's assertion of inherent disclosure is improper.

A rationale *must* be supplied on the record in order for the PTO to establish a *prima facie* case of obviousness. MPEP §§ 2141, 2145. The Examiner's assertions (items (i)-(iii) above) are devoid of any evidence or reasoning as to why, without impermissibly relying on the teachings of the instant application, a person having ordinary skill in the art would have expected *any* "alternative gel material" not only to serve as a substitute for the acrylamide of Mitra, but also to provide a nucleic acid amplification of enhanced sensitivity, *with the requisite reasonable expectation of success*.

Gellan-enhanced PCR sensitivity could not have been predicted from the prior art, and the PTO fails to provide even a scintilla of evidence that the prior art suggests a nucleic acid amplification reaction is more sensitive when gellan is present than when gellan is absent. The test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art. MPEP § 2143.01[III]. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. MPEP § 2143.01[III] (citing *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1396 (2007)).

The PTO also clearly errs in the allegations found at page 4, lines 6-12 of the Action. The Examiner impermissibly rejects as obvious applicant's discovery that gellan can enhance the sensitivity of a nucleic amplification reaction, despite knowledge in the prior art that gellan inhibits such reactions by virtue of its affinity for divalent cations just as other chelating

agents (*e.g.*, EDTA) were known to inhibit nucleic acid amplification reactions. The Examiner errs in asserting that applicant's specification "clearly speaks to gel formation, not when the gel has already been formed" and that "[w]hile chelating agents can solubilize a formed gellan gel, this does not demonstrate that addition of further divalent cations are taken up by the gellan gel."

Briefly, knowledge in the prior art and evidence of record indicate that a formed gellan polymer sequesters divalent cations at least as strongly as does an EDTA concentration that is known to inhibit PCR reactions. In direct contradiction of the Examiner's allegations, the prior art recognized that even an *already-formed* gellan gel can *further* sequester additional divalent cations, as explained in applicant's submission of February 9, 2009, at page 6, first full paragraph, through page 8, first paragraph. The skilled person would thus reasonably have believed that gellan would inhibit a nucleic acid amplification reaction by chelating divalent cations, as does EDTA.

Additionally, the Examiner's alleged rationale (iii) (reversibly forms gels) for asserting the combination of Cole et al. with Mitra et al. is technically flawed because the method of Mitra et al. depends on an immobilized primer that is covalently and irreversibly incorporated into the acrylamide gel by free radical-mediated chemical crosslinking, as discussed in applicant's submission of February 9, 2009, at page 5, line 25 through page 6, line 14. Therein can also be found discussion of PTO error in alleging that gellan of Cole and acrylamide of Mitra are interchangeable equivalents, because the PTO fails to meet its burden of showing that such an assertion of equivalency must be recognized by the prior art as being equivalency for the same purpose. MPEP §2144.06, citing *In re Ruff*, 256 F.2d 590 (CCPA 1958).

Respectfully submitted,

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